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by

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INDICATIONS FOR SURGERY IN THE TREATMENT OF GASTRIC AND DUODENAL ULCERS*

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THE end results from both medical and surgical treatment of ulcers are frequently poorly understood by both the internist and the surgeon because they lack the opportunity for a long period of observation of the results of both methods. The life cycle of an ulcer is long and the flare-ups of pain and massive hemorrhage cause the patient to become discouraged or alarmed and frequently he seeks the advice of another physician, or more likely a surgeon, as the one to offer permanent relief. Having spent over 18 years in the Ulcer Clinic of the 4th Division at Bellevue Hospital and 7 years in the Ulcer Clinic at Post-Graduate I believe I can see more clearly the advantage of both methods of treatment and I shall present my deductions today.

The patient suffering from a gastric ulcer is more likely to be advised operation than a patient with a duodenal ulcer. The danger of malignant degeneration is the motivating factor in the choice of surgery for most cases of gastric ulcer. The incidence of the development of

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malignant changes is quoted variously as 1 per cent to 70 per cent. The pathologists have had difficulty in the differential diagnosis of some of the gastric lesions as Cole[1] illustrated 10 years ago. These are the same cases which the roentgenologist, the gastroscopist and the clinician have difficulty in accurately diagnosing. The clinical course of an ulcer of the stomach has a most important bearing on the indications for operation. In some cases it is difficult to distinguish a gastric ulcer from a carcinoma. In 8.5 per cent of our cases[2] we could not be certain of the diagnosis and an immediate operation was advised, but in this group 75 per cent were found to be ulcers upon histologic study following sub-total resection. This does not prove that a gastric ulcer becomes a carcinomatous lesion, but in a small group of cases we have no accurate method of differentiating between the two lesions. My views on this point coincide with the opinion expressed by Palmer[3] that the existence of carcinomatous degeneration in a benign ulcer remains to be proved conclusively. The United States Bureau of Census states that there were 6,390 deaths from gastric ulcer in 1943 and 2,943 deaths from duodenal ulcer. These figures are hard to reconcile since gastric ulcers constitute only about 10 per cent of the total number of ulcers encountered. In our clinic at Bellevue Hospital we found[4] that of 1,256 ulcers 89 per cent were duodenal and 11 per cent gastric.

In the stomach clinic of the 4th Medical and Surgical Divisions at Bellevue Hospital, which is entering its 19th year, we have adopted the policy that a gastric ulcer will respond to medical management as satisfactorily as will a duodenal ulcer, and in most instances it is easier to heal a gastric ulcer than a duodenal ulcer on a dietary regimen. The mistakes in following such a policy are few compared with the mortality from sub-total resection of gastric ulcers in the hands of the average surgeon. Any one doing a reasonable amount of gastric surgery can have a low mortality. The author has just reported[5] 162 cases of primary duodenal ulcer with 6 deaths, or 3.7 per cent mortality, and 85 cases, 22 per cent of which were gastric ulcers in which a sub-total gastrectomy was performed, with a mortality of 3.5 per cent.[6]

From 1920 to 1944 inclusive there were 806 ulcer admissions on the Medical and Surgical services of Post-Graduate Hospital 112 of which were gastric ulcers, 13.8 per cent of the total. It is interesting to review these cases as they came under the care of a large number of doctors during the 25 year period. Private cases are not included in this dis-

cussion. In the early part of this period local excisions and gastroenterostomies were performed for gastric ulcers. In 43 cases sub-total resections were done, with 11 deaths or a 25.5 per cent mortality. Thirty-three gastric ulcers were treated medically, with no deaths, but one of these patients was subsequently admitted with carcinoma one year after the first admission. In reviewing the history of this case it would seem that the patient had a carcinoma originally. There were 12 cases of gastric carcinoma in which there was a question of its arising on a pre-existing ulcer. These cases are included in the 112 ulcer cases and constitute 10 per cent of the total gastric ulcer admissions over the 25 year period. This is not high when we remember that gastroscopy was not employed in the early cases and our roentgen studies were not as accurate as they are now.

In two cases it might be argued that the ulcer developed into a carcinoma. One of these patients, a man 45 years of age, was admitted in January of 1925 with a five weeks' history of upper abdominal discomfort. The gastrointestinal x-ray series revealed a gastric ulcer on the lesser curvature in pars media and a Balfour excision and a gastroenterostomy were done. The patient was re-admitted in February 1941 with a carcinoma of the stomach which involved a pyloric portion on the greater curvature. Whether this carcinoma arose from the original ulcer or whether it was a separate growth cannot be proven, but it would seem that after a period of 17 years, in all probability the carcinoma was not related to the original ulcer. The second patient was a man 48 years of age admitted in January 1933 with an 8 year history of stomach trouble. He was found to have a pyloric ulcer and a gastroenterostomy was performed. In January 1939 he was re-admitted with an inoperable pyloric ulcer. These two cases, and the medically treated patient re-admitted with carcinoma of the stomach one year later, which was apparently an undiagnosed primary carcinoma, constitute the only clinical proof we have of the danger of carcinomatous degeneration.

The interesting question is whether sub-total gastrectomy should be so freely recommended in cases of gastric ulcer to prevent malignant degeneration when the procedure in the hands of the average surgeon carries such a high mortality. In this group of cases covering a 25 year period the 25.5 per cent mortality comes nearer to approximating the mortality in the average hospital than do figures given from large medical centers which represent the experience of a small group of highly

trained gastric surgeons.

The decision as to conservative management or operative intervention in duodenal ulcers is usually dictated by the probability of operative mortality if surgery is advised.

Duodenal ulcers, if diagnosed early, will respond very satisfactorily in most instances to a medical regimen. A small percentage, even with adequate medical care, will become intractable or recalcitrant. The great difficulty encountered by both internist and surgeon is in differentiating between exacerbations of a chronic duodenal ulcer and intractability which necessitates operation. The patient with a chronic duodenal ulcer may become discouraged during a period of exacerbation and seek the advice of a surgeon. Frequently the surgeon mistakes an exacerbation for chronic intractability and if an operation is performed the end results will often prove disappointing, while the end results from sub-total resection for intractability prove most gratifying.

The duodenal ulcer which penetrates the posterior wall and becomes adherent to the pancreas can no longer be treated medically and becomes a surgical problem. Also, any duodenal lesion which has completely penetrated the wall of the duodenum and is adherent to an adjacent viscus, whether it be the gall bladder, the liver or the duodenohepatic ligament, is a true surgical problem and sub-total resection should always be performed with removal of the ulcer *in toto*. Gastroenterostomy will prove most disappointing in this type of case. In a previous review[7] of gastroenterostomies for intractable duodenal ulcers we found only 24.5 per cent of cures in 106 cases followed for 7.1 years. Of course if a gastroenterostomy is performed early, before the complications of the long standing ulcer have arisen, the results will be much better, but these patients can obtain symptomatic relief on an adequate medical regimen.

Continuous pain with the x-ray findings of a penetrating lesion in the duodenum will suffice to differentiate between the intractable ulcer necessitating operation and the exacerbation which will subside with adequate medical care. However, there is one type of duodenal ulcer which is difficult to diagnose and which will not respond to a medical regimen, and that is the ulcer on the pyloric sphincter. This ulcer causes extreme pain and frequently the gastrointestinal series will show, not a true penetrating lesion, but a marked pylorospasm. In this instance a sub-total resection should be done with removal of the lesion. This type

of ulcer is similar to a fissure in ano, and, as is well known, the anal fissure causes pain out of proportion to the pathology found.

In the past 13 years I have not performed a gastroenterostomy for any type of ulcer. The so-called pyloric obstruction without pain will always respond to gastric lavage, anti-spasmodics, and dietary management. There are cases of pyloric obstruction which will not respond to a medical regimen, but these patients have a penetrating ulcer with associated pain. Gastroenterostomy in this type of case will prove most disastrous because the active duodenal ulcer remains unhealed and gastrojejunal ulcer is a frequent sequela.

Massive hemorrhage always presents a problem in the treatment of peptic ulcer. Conservative treatment in these cases is attended with a definite mortality.

In 135 cases of massive hemorrhage treated on the 4th Division at Bellevue Hospital from 1928 to March 1937 inclusive there was a 12 per cent mortality under conservative treatment.[8]

Hospitals without an active ambulance service see very few patients with exsanguinating hemorrhages because of the severity of the condition, and with the alarming feature of vomiting large quantities of blood, an ambulance is usually called immediately. The patient admitted with a severe gastric hemorrhage should have a blood grouping immediately and a transfusion started. Hemorrhage is caused either by a venous ooze or by erosion of a large artery. Most bleeding ulcers are duodenal, since 90 per cent of all ulcers are duodenal. A gastric ulcer may have a large artery at its base but massive hemorrhage from a duodenal ulcer results from erosion of the superior pancreatico-duodenal artery or one of its large branches by the ulcerating process. An arterial hemorrhage will prove fatal unless controlled while a venous ooze will respond to conservative treatment.

Surgery is employed occasionally as a life-saving measure, but these instances should be few in a large series of cases. Most massive hemorrhages can be controlled by transfusion and conservative measures. The problem is to determine which case will continue to bleed. We have used the transfusion test as the best means of determining which patients have arterial hemorrhages necessitating operation as against those with venous ooze. A continuous transfusion is given by the indirect method and if after receiving 1500 to 3000 cc. of blood the patient remains in shock, it is very likely that the superior pancreatico-duodenal artery is

eroded through, if it is a duodenal ulcer, or that a large artery is eroded in the crater of a gastric lesion.

Whether conservative treatment should be continued after recovery from the massive hemorrhage, or whether an elective operation should be performed, depends upon the x-ray findings and the clinical course. If the patient is free from pain, then surgery is seldom indicated regardless of whether it be the second or third massive hemorrhage. We practically never advise operation as an elective procedure for a patient who has recovered from a massive hemorrhage unless he is suffering from uncontrollable pain.

The first sub-total resection for severe uncontrollable hemorrhage done on the 4th Division at Bellevue Hospital was performed by me on a 27 year old man in March of 1937. In this case the ulcer had eroded through the superior pancreatico-duodenal artery which was sutured after sub-total resection, and the patient recovered.

From 1937 to 1945 inclusive we have had 142 cases of massive hemorrhage on the 4th Division at Bellevue Hospital. Of these, 104, or 73 per cent were not operated upon. Thirty-eight operations were performed, 14 of which were emergency procedures. Among the 24 elective operations, there was one death, a mortality of 4 per cent; among the 14 sub-total resections performed as a life-saving procedure, there were 5 deaths, a mortality of 35 per cent. In the 104 unoperated cases there were two deaths, a mortality of 2 per cent. The total number of deaths in the operated and unoperated cases was 8, a mortality of 5.6 per cent. This reduces the 12 per cent mortality of the 1928-1937 group by half.

From 1920 to 1944 inclusive, 115 cases of massive hemorrhage were admitted to Post-Graduate Hospital. This hospital does not have an ambulance service, so the type of case is not as severe. Eighty-two of these 115 patients received conservative treatment. Thirty-three, or 28 per cent were operated upon, but not during the acute hemorrhage. Seven, or 21 per cent, died as the result of the operation. Of the 26 patients living, 12, or 46 per cent, were re-admitted for subsequent hemorrhage. Of the 82 patients treated conservatively 15, or 18 per cent, were re-admitted for massive hemorrhage but they were not operated upon. One died, a mortality of 1.2 per cent. We may conclude that in these cases the hemorrhage on admission was not severe and that those patients who were advised operation might possibly have done better

with conservative treatment. When we compare the mortality and the re-admissions in the two groups, we can see the great advantage of having a group of internists and surgeons dictate the policy in the treatment of massive hemorrhage.

Conclusions

1. In not more than 10 per cent of gastric ulcers should there be a question as to the diagnosis. In the questionable cases an immediate operation should be advised.

2. Gastric ulcers respond more readily to medical management than do duodenal ulcers. The mortality from routine sub-total resections for gastric ulcer far exceeds the possibility of malignant degeneration in unoperated cases. Only those duodenal ulcers which fall in the chronic intractable group should be operated upon.

3. So-called pyloric obstruction is not an indication for operation.

4. Massive hemorrhage in the majority of cases should be treated conservatively with blood transfusion. There is a definite mortality with conservative management alone; in our experience it has been as high as 12 per cent. Sub-total resection is indicated occasionally as a life-saving procedure. Our mortality has been reduced by half in the past 9 years by using it in selected cases. An elective operation should not be advocated for patients who have recovered from a massive hemorrhage unless they have associated pain. Patients operated upon for painless massive hemorrhage are frequently re-admitted with subsequent massive hemorrhage even after sub-total resection.

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OBSERVATIONS ON THE DYNAMICS OF THE SYSTEMIC CIRCULATION IN MAN*

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THE dynamics of the systemic circulation is a very large and complex subject, involving not only blood flow as a whole, under the various existing levels of vascular pressure throughout the circuit, but including also all the local and regional conditions of pressure and flow, each with its own independence of action, yet each influencing and itself a part of the adjustment of the whole system.

My discussion this evening will not attempt to cover this field, but will be restricted to the circulation as a whole, in man; that is, the behavior of blood in the systemic great vessels and the heart. It will be concerned particularly with the contributions to this subject which have been made during the last four years by the technique of right heart catheterization.[1] Dr. Cournand's paper, which follows, will describe the contributions which have been made similarly to the knowledge of the pulmonary circulation.

The chief methods used have been, first, the determination of cardiac output, by the familiar Fick principle[2] and second, the continuous recording of pressures, in heart and great vessels, by optical registration.[3]

The so-called direct Fick principle depends upon direct determination of three values, oxygen in arterial blood, oxygen in mixed venous blood, and total oxygen intake per minute. Cardiac output is obtained by dividing oxygen intake per minute by the arteriovenous oxygen difference. This method of cardiac output determination is now generally accepted as the most reliable in human subjects.

As is well known, there has been for many years a controversy over the value of resting cardiac output in man. Earlier methods gave values of 5 to 6 liters per minute. In the last decade, the accepted foreign gas methods gave as a normal average 2.2 liters per square meter of body surface, or between 3.5 and 4.0 liters per minute.[4]

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TABLE I

BLOOD FLOW THROUGH VARIOUS ORGANS AND REGIONS OF THE BODY, IN MAN AT REST

Brain	900	cc./min.
Kidney	1300	"
Liver	1300	"
Extremities	1800	"
	5300	"
Lungs (cardiac output)	5400	"

By the catheterization technique, in the hands of several independent investigtaors,[2, 5, 6] the average cardiac output of the normal subject at rest is approximately 5.4 liters per minute, or 3.1 liters per square meter of body surface.

As pointed out by Hamilton,[7] this figure fits better with that obtained when one adds together the blood flows through special organs and regions of the body. This is indicated in Table I. The cerebral blood flow figure is that of Schmidt,[8] renal flow obtained by Smith's renal clearance method,[9] hepatic flow by an interesting method developed by Bradley,[10] in which he catheterizes one of the hepatic veins, and measures hepatic clearance or removal from the blood of bromsulfalein. The agreement in the table is not perfect as no account is taken of such regional blood flows as the coronary, thyroid, adrenal, and intercostal; but it is reasonably good.

Another controversial question has been that of cardiac output alteration with change of posture. Earlier investigators using indirect rebreathing methods found cardiac output depressed in the sitting or standing as compared with the recumbent position. With the ethyl iodide and acetylene methods no significant difference was found.[4] McMichael and Sharpey-Schaefer[6] using right heart catheterization, found in fourteen subjects unequivocal evidence that the cardiac output is less in the upright than in the recumbent position, the average decrease being 34 per cent.

When both total flow and initial and final pressures are known in a fluid-filled system of tubes, it should be possible to describe the resistance along the system. The circulation of the blood, however, is

TABLE II—NORMAL CIRCULATION

	Rest	*Moderate Exercise*
Pulse Rate, per min.	60	150
Cardiac Output, liters/min.	5.4	20
Arterial Pressure, mm.Hg.	120/80	160/95
Venous Pressure (arm), mm.Hg.	4	10
Right Auricular Pressure, mm.Hg.	2	?

extraordinarily complex. Blood is not a homogeneous fluid but a suspension; in the smallest capillaries each cell often distending the vessel as it moves along. The flow is pulsatile in the arteries, steady in the veins. The channels of flow are elastic; arteries, capillaries and veins having different distensibilities, and being subject to large and unpredictable nervous or vasomotor effects. No law of flow has been devised that will describe so complicated a system.

There is, none the less, some usefulness in the general concept of peripheral resistance. This is, essentially, the average rate of fall of blood pressure around the circuit, per unit of blood flow. It is expressed as a simple ratio, mean arterial pressure divided by cardiac output. The general significance of this ratio is obvious: a high arterial pressure and a small cardiac output means a high peripheral resistance, a low arterial pressure with a large output means a low resistance. Table II gives some normal figures of the circulation at rest and in moderate exercise. The peripheral resistance at rest would be represented by mean arterial pressure, about 90 mm.Hg., divided by cardiac output 5.4, or a figure of 14; in exercise, a mean pressure of, say, 120, divided by 20, or a figure of 6, indicating the extent of vasodilatation in exercise. In current usage, the term is usually expressed in dynes per cm.$^{-5}$ per second, which gives normal values between 1000 and 1500.

An interesting study in this connection is that recently carried out in Dr. Cournand's laboratory, in collaboration with Drs. Chasis and Goldring, the measurement of blood flow and pressures in five cases of essential hypertension both before and following bilateral sympathectomy. The results are summarized in Table III. The patients had high

TABLE III

EFFECT OF BILATERAL SYMPATHECTOMY UPON CARDIAC OUTPUT AND PERIPHERAL RESISTANCE IN 5 CASES OF ESSENTIAL HYPERTENSION

	Body Surf. Area	*Mean Art. Blood Press. mm.Hg.*	*Cardiac Output per minute* lit.	lit./ sq.m.	*per beat* cc.	*Periph. Resist.*	*A-V Dif.* cc./ lit.	*02 Intake* cc/min. /sq.m.	*Pulse Rate*
Average before operation	1.68	160	5.70	3.39	70	2250	41	138	82
Average after operation	1.60	135	5.52	3.45	64	1960	38	131	87

TABLE IV

VARYING EFFECTS OF METHEDRINE ON THE CIRCULATION

Subject	*Time*	*Pressures, mm.Hg. Arterial (femoral)*	*Right Syst.*	*Ventricle Diast.*	*Right Auricle*	*Cardiac Index, liters*	*A-V Dif.*	*Periph. Resist.*	*Pulse Rate*
F.K. Female, 33; normal	0	127/65	25	4	—	2.47	3.9	1760	60
	0	125/62	21	1	—	2.34	4.0	1770	58
		Methedrine, 30 mg. intravenously							
	4′	209/94	43	5	—	—	—	—	—
	18′	195/89	65	6	—	2.64	4.2	2440	62
J.T. Male, 30; lac. scalp, 15% blood loss, acute alcoholism	0	63/34	—	—	2	2.81	5.0	620	59
		Methedrine, 30 mg. intravenously (6 hrs. after injury)							
	7′	95/53	—	—	—	—	—	—	—
	36′	98/56	—	—	3	3.98	3.9	700	100
	134′	91/50	—	—	—	3.98	4.1	630	96
J.K. Male, 53; phlebotomy, 20% of blood volume	0	58/37	—	—	1	1.81	8.1	1410	104
		Methedrine, 30 mg. intravenously							
	5′	80/50	—	—	—	—	—	—	115
	10′	86/55	—	—	—	—	—	—	140
	58′	87/56	—	—	—	1.73	7.2	2330	133

blood pressures but normal cardiac outputs before operation. Sympathectomy caused no change in output, the result being solely that of reduction in arterial pressure, and correspondingly, in peripheral resistance.

The reverse change is seen in the effects of the sympathomimetic drug methedrine on the normal circulation. As Table IV shows, there is a sharp rise in arterial, also in right ventricular pressure, but no change in cardiac output, peripheral resistance increasing from 1770 to 2440.

Quite different is the response to this drug in a patient in moderate shock, who was also acutely alcoholic, with the characteristic vasodilatation and hypotension produced by alcohol, also shown in Table IV. In this case methedrine brought about an increase in both arterial pressure and cardiac output, together with a striking clinical improvement. This illustrates a principle often overlooked, that a drug may have quite a different effect under pathological conditions from what it does under normal conditions.

Before considering pressure relations in the great veins, leading up to and including intracardiac pressures, one should perhaps emphasize again the primary fact that while the heart is an effective pump, it can eject only as much blood as reaches it by way of the venous return. This physiological principle was established many years ago by Krogh, Yandell Henderson, and others.

The pressures in auricle and ventricle in the normal cardiac cycle have been extensively studied in dogs by Wiggers and others. Such pressures in man are similar, as recently demonstrated by Bloomfield et al.[3] Figure 1, A is a continuous recording of auricular pressure through a number of cardiac cycles, in a normal subject. The electrocardiogram is at the top of the record, the arterial pressure next (obtained from an indwelling needle in the femoral artery), and below this the right auricular pressure. As recorded here, the first event in the cardiac cycle is the P-wave of the electrocardiogram, followed very shortly by the beginning of the auricular pressure rise caused by auricular systole (line 1 on tracing). Auricular systole, some 4 mm. or 5 mm. in amplitude, rises to its peak and declines (1 to 2 on tracing). The subsequent small nick, or momentary rise in the auricular record (2 to 3 on tracing) corresponds to the onset of ventricular systole. This is found on animal records and is generally agreed to be the quick bulging backward of the tricuspid valve. The subsequent sharp drop (beyond line 3) in

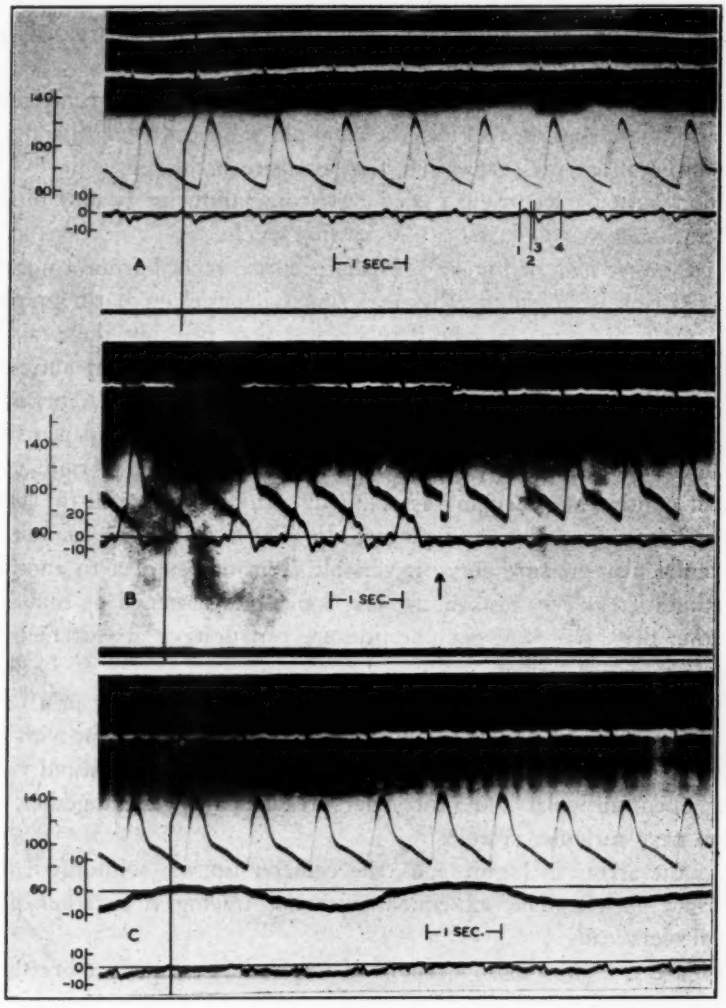

Figure 1. Pressure tracings in normal human subjects. Section A, from above downward: electrocardiogram, femoral arterial pressure, right auricular pressure. Vertical line indicates identical times on the three tracings. For explanation of points 1, 2, 3, and 4, see text. Section B: electrocardiogram, femoral arterial pressure, right ventricular pressure in first half, right auricular pressure beyond arrow. Section C: similar to A, except for intrapleural pressure tracing (inspiration up, expiration down) between tracings of femoral artery and right auricle.

auricular pressure is due to the "descent of the base" of the heart, the whole tricuspid region moving downward as ventricular contraction is completed with upward ejection of blood into the pulmonary arteries. The subsequent steady rise in auricular pressure up to line 4 is due to venous inflow, with tricuspid valve still closed. At line 4 ventricular relaxation has progressed so that the tricuspid valve opens, with another drop in auricular pressure. After this, pressure builds up again in the common auricular-ventricular chamber from inflowing venous blood, until auricular systole starts a new cardiac cycle.

In the first half of Figure 1, B the pressure record from a normal right ventricle is shown, together with simultaneous electrocardiographic and arterial pressure tracings. The vertical line, marking the peak of auricular systole (just as in Figure 1, A above), shows that auricular systole causes a small upward wave in ventricular pressure. This is to be expected since the tricuspid valve is open and auricle and ventricle form a common chamber. Next comes the sharp rise due to right ventricular contraction, reaching a maximum systolic pressure in the lesser circuit between 18 mm. and 30 mm.Hg. The form of the summit of the ventricular pressure curve is variable from one subject to another, sometimes irregularly peaked, as here, sometimes flattened or rounded. Whether these represent genuine pressure variations or are artefacts of recording, is not known.

Ventricular relaxation, as shown, is also rapid, resulting in a drop of pressure ending in a "dip" which is practically synchronous with the auricular dip seen after line 3 in Figure 1, A above. The tricuspid valve being open, auricular and ventricular pressures then rise together, up to the next auricular systole.

At the arrow in Figure 1, B, the catheter tip was withdrawn into the right auricle. The subsequent auricular tracing is a rather poor record technically.

Figure 1, C shows also a record of respiration, the patient breathing in this instance somewhat rapidly and deeply. The effect of this on both the amplitude and basic pressure level of the auricular tracing, is well brought out.

Mean pressure in the right auricle in most normal subjects varies between a level 2 or 3 mm. Hg. above to the same amount below an arbitrary zero level, this latter being taken on these records as 5 cm. below the angle of Louis, with the subject lying recumbent.

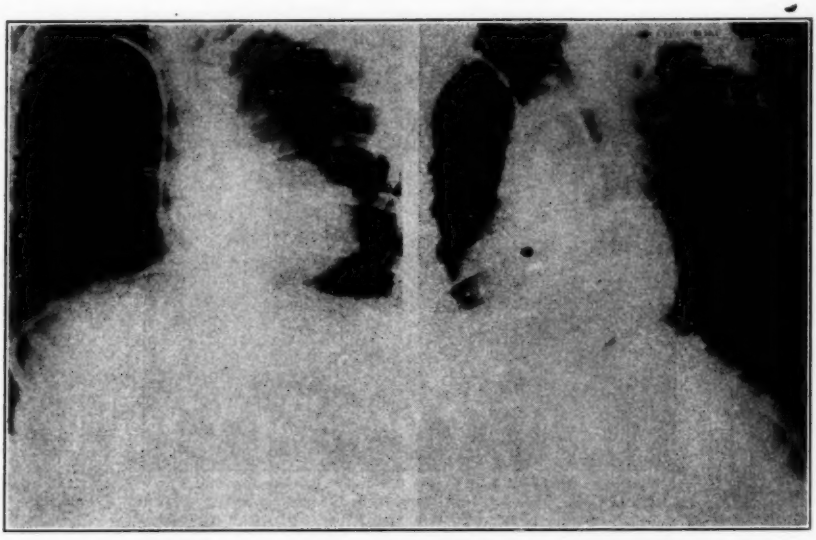

Figure 2. Catheter passed into right auricle, right ventricle, through septal defect, and around aortic arch.

Such is a brief description of the pressure changes within the right heart during the cardiac cycle.

On the venous side of the circulation, one other normal phenomenon may be mentioned, namely, the pressure difference or pressure gradient between arm vein and right auricle. This difference is variable but averages about 40 mm. of water.[11] This arm to heart gradient, as Ferris has shown,[12] is due largely to the collapse of the larger peripheral veins in the resting state.

Variations in right ventricular pressures in physiological and pathological conditions are concerned more immediately with the pulmonary circulation and will be discussed by Dr. Cournand in the succeeding paper.

One additional tracing might perhaps be shown, a pressure record in a human aorta. This was a paient with septal defect catheterized recently by Dr. Cournand, the catheter passing through the defect and on around the aortic arch. Figure 2 shows the catheter in the aorta, and Figure 3 the intra-aortic pressure tracing.

Peripheral circulatory failure, or shock, in its various forms, has received intensive study during the war, by these as well as other meth-

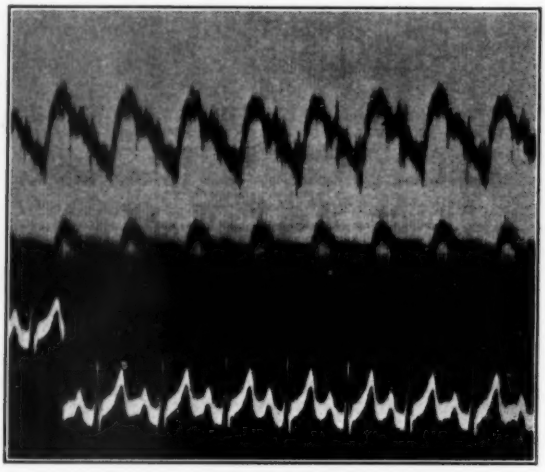

Figure 3. Intra-aortic pressure tracing (above) from case shown in Figure 2. The record is distorted by vibrations. Below is a femoral artery tracing, much damped, and below this the electrocardiogram.

ods; and only the briefest review is indicated in this discussion. Perhaps the most significant addition to our concept of peripheral circulatory failure is that there are a number of specific types, each with its own pattern of circulatory disturbance.[13]

The standard form, so to speak, of secondary shock is that produced by skeletal trauma or hemorrhage, presented in chart form in Figure 4. Here trauma and hemorrhage are compared with the normal in blood and red cell volume, cardiac output, auricular pressure, arterial pressure, and peripheral resistance. The basic loss here is whole blood, with red cells further down than serum; the low blood volume leading to decreased venous return, decreased cardiac output, decreased arterial pressure.

Figure 5 shows an arterial pressure tracing in advanced shock, compared with the normal. The low systolic level, and collapsing quality, are apparent, indicating an essentially empty vessel. Figure 6 shows an arterial and a right ventricular tracing after acute blood loss, with gradual recovery over several hours following intravenous fluid. The small ventricular complex is indicative of poor cardiac filling.

The shock seen in severe burns has quite a different pattern (Figure 7). There is of course hemoconcentration, loss of blood volume, and

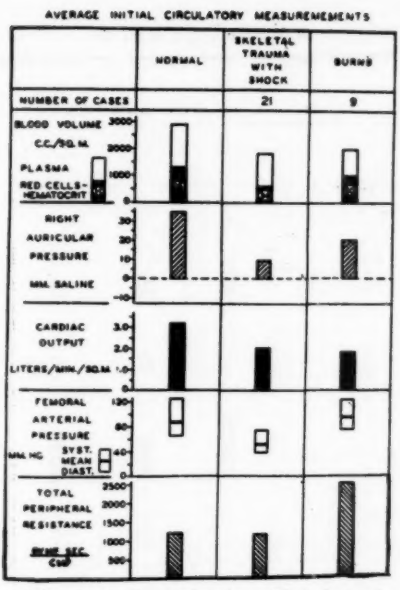

Figure 4. Chart showing chief dynamic changes in the circulation in traumatic and hemorrhagic shock.

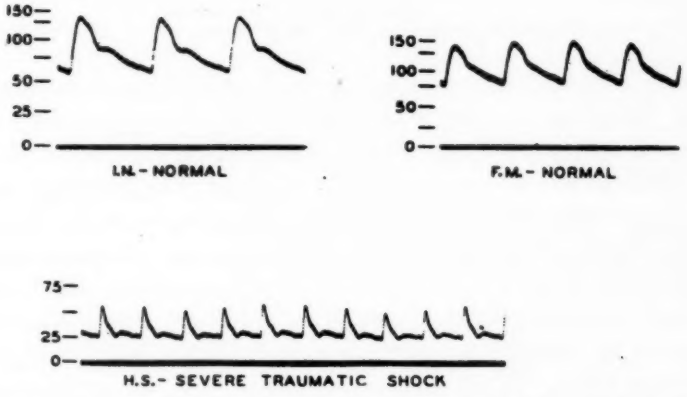

Figure 5. Femoral artery pressure tracings in normal subjects and in shock.

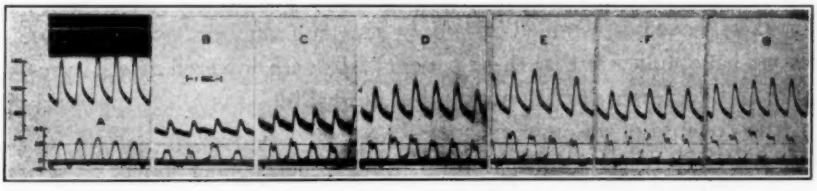

Figure 6. Tracings from femoral artery and from right ventricle in a normal subject before and after a large phlebotomy. A = before; B = immediately after. Patient was pale and in shock. Cardiac output was 40 per cent of normal. C, D, E, and F = progressive stages in recovery during and following an intravenous infusion of gelatin solution. G = 4 hours after phlebotomy, cardiac output then 95 per cent of normal.

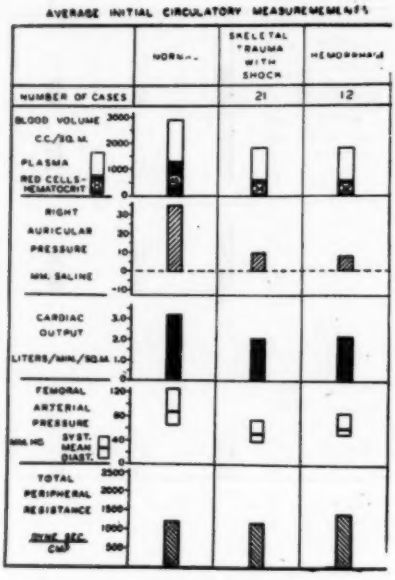

Figure 7. Chart showing chief hemodynamic changes in shock due to burns.

markedly decreased cardiac output. But right auricular pressure is maintained, sometimes even elevated, and arterial pressure is usually also maintained or elevated, sometimes almost to the moment of exitus. Peripheral resistance is thus markedly increased. This has been found even in cases seen very early before hemoconcentration set in. That the normal or high auricular pressure was not due to heart failure was shown by rapid subsidence of venous pressure as well as relief of shock, upon the rapid administration of plasma. Thus a primary reaction in burns appears to be intense vasoconstriction, both arterial and venous, with circulatory failure due not so much to failure of venous pressure as to failure of filling of great vessels, and of the heart itself.

Cases of so-called medical shock, seen in pneumonia, for example, or sepsis, have been studied but not in adequate numbers. Such evidence as we have indicates that these patients fail, with lowered arterial pressure and decreased cardiac output, but normal blood volume, apparently a true collapse of vasomotor tone.

We have better information on primary neurogenic shock, or syncope. This has been studied by Stead and by McMichael, in normal

TABLE V

DYNAMICS OF DIFFERENT FORMS OF SHOCK

	Trauma Hemorrhage	*Burns*	*Medical Shock*	*Syncope*
Cardiac Output	—	—	—	±
Periph. Resistance	±	+	—(?)	—
Blood Volume	—	—	±	±

individuals subjected to a quick phlebotomy. During the phlebotomy McMichael found cardiac output and auricular pressure slightly decreased. Stead also found auricular pressure decreased but no change in cardiac output. This may have been due to different speed of blood removal. When the subject actually fainted, however, both investigators agreed that with the profound drop in arterial pressure, there was no further decrease in the cardiac output. In Stead's cases, auricular pressure even increased. McMichael also measured blood flow in the arm during the faint, and found this increased. The conclusion is that the essential failure in syncope is sudden loss of vasomotor tone in the blood vessels of skeletal muscles.

Table V gives in schematized form the different patterns of circulatory failure in four major types of shock.

Finally I should like to present a few observations on the dynamics of congestive heart failure. While this has been investigated extensively in recent years (Harrison[14]), there are many unanswered and controversial questions.

It has been generally agreed that as the heart muscle begins to fail, there occurs first an inadequate ventricular emptying, this leading both to dilatation and to increased diastolic filling pressure; and that this may exist even while the cardiac output remains normal. As cardiac insufficiency progresses, cardiac output usually becomes diminished; but catheterization studies have confirmed earlier work that advanced congestive failure may exist in the presence of normal or even increased cardiac output, as for example when associated with anemia, fever, or hyperthyroidism.[15, 16] Thus the essential feature of congestive failure is more one of pressures than of flow.

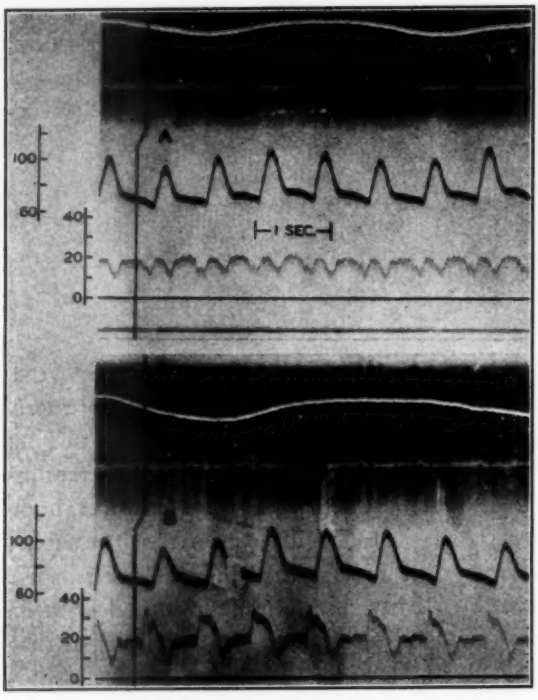

Figure 8. Pressure tracings in a patient with right-sided failure (constrictive pericarditis). Upper curve, pneumograph, next electrocardiogram, next femoral artery pressure, at bottom pressure in right auricle (Section A) and right ventricle (Section B).

Intracardiac pressure records bring out clearly the pressure abnormalities in congestive heart failure. Figure 8, A gives the auricular pressure tracing in a patient with right-sided congestion. (This particular case was one of constrictive pericarditis.) The contrast to the normal record (Figure 1, A) is apparent. The basal or diastolic level of auricular pressure is of course elevated, around 20 mm.Hg. or 260 mm. of saline. Auricular systole is only faintly recorded in this case. With the descent of the base early in ventricular systole there is a marked drop in auricular pressure, followed by a rapid rise again, as blood comes in from the distended great veins to fill the auricle. With ventricular relaxation, at the opening of the tricuspid valve, there is again a sharp drop in auricular pressure, followed by a rapid rise. The whole picture is that of a dis-

tended chamber under increased pressure, with two momentary periods of pressure release. The W-shaped auricular pressure curve is characteristic of the congestive state. Figure 8, B gives the corresponding right ventricular tracing. The sharp "diastolic dip" with ventricular relaxation is again evidence of a distended (auricular) chamber, followed by sudden release of pressure, followed in turn by rapid filling both of auricle and of ventricle and return to high venous and intracardiac pressure.

A further problem of interest is the mechanism of development of edema in congestive heart failure. The original theory of Starling held that "backing up" of pressure in the great veins led, by way of retarded blood flow through the bone marrow, to increased blood volume, the systemic venous bed thus becoming distended with fluid, which escaped into the tissues. Warren and Stead[17] found, in resting cardiac patients, that with increased fluid intake, blood volume increased before any rise occurred in venous pressure. More recently, Merrill[18] has shown, both that renal blood flow is greatly decreased (to one-third normal) in congestive failure, and that there is a good correlation between renal blood flow and cardiac output, but no correlation between renal blood flow and venous pressure. Stead and his colleagues advance the theory that edema in congestive failure is primarily a renal failure to excrete salt and water, caused by a cardiac output inadequate to body needs, and secondarily a decreased renal blood flow. Landis[19] stresses the importance of considering venous pressure in cardiacs during stress as well as at rest, and shows that in dogs with experimentally damaged hearts increasing the load on the heart will send it into frank congestive failure with abnormally increased venous pressure, whereas at rest no failure was demonstrated. Still further evidence is probably needed to decide this question.

There is one form of heart failure which can be diagnosed rather accurately by pressure tracings. This is congestive failure with tricuspid insufficiency. Figure 9 gives a tracing obtained in such a case. In this instance a double-channeled catheter was used, with one opening at the tip and the other about 10 cm. back of the tip, so that when the tip is in the right ventricle, the second opening is in the auricle.

The characteristic feature here is that in the lower or auricular tracing the first dip of the W is absent. Instead of the descent of the tricuspid valve in early ventricular systole, blood spurts back into the

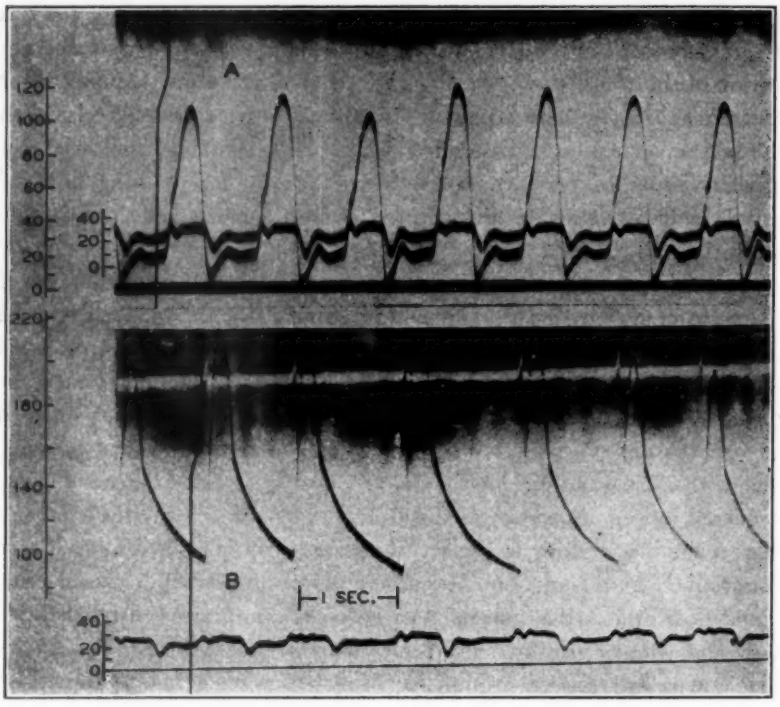

Figure 9. Simultaneous right auricular and right ventricular tracings (Section A) in a case of tricuspid insufficiency. See text.

auricle, and auricular pressure continues unchanged or even rises slightly.

So far as concerns the relation between the pressures in peripheral and central veins in congestive failure, it was found early in the course of catheterization studies,[11] that the normal gradient of 30 to 40 mm. of water between arm and heart disappears, and in congestive failure, peripheral and central venous pressures become practically identical. This is probably due chiefly to venous distention, with larger channels of flow between arm and heart.

As a last observation I should like to mention some interesting work by McMichael and Sharpey-Schaefer[20] on the action of digitalis, or more specifically of intravenous digoxin on the pressure and output of the heart in congestive failure. It is of course well known, from a number of earlier investigations, that digitalis decreases both heart size and cardiac output in normal subjects, whereas in dilated failing hearts

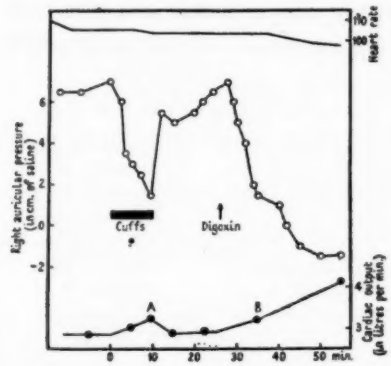

Figure 10. From McMichael and Sharpey-Schaefer (see text). Variations in heart rate, right auricular pressure, and cardiac output produced in a patient with congestive heart failure by cuffs on the extremities and by digoxin.

digitalis decreases heart size but increases output. McMichael confirmed this, but noted also a very marked and prompt drop in right auricular pressure as an early action of digoxin. The whole effect was quite comparable to that of phlebotomy or of cuffs applied to the extremities, in these patients. The chart of a typical case, from McMichael's paper, is shown in Figure 10. These results indicate a strong peripheral action of digoxin, opening up some as yet unidentified venous depots, permitting venous pressure fall, and thus relieving the congested heart. It may be noted, however, that a direct action on heart muscle, by producing better cardiac emptying, would also decrease auricular pressure and increase cardiac output.

This study of McMichael's with digitalis is a further illustration of the manner in which the effects of drugs on the circulation can be studied; and there would appear to be an excellent opportunity to investigate most of the rapidly acting cardiovascular drugs by this means.

Summarizing these rather scattered observations, one may say that catheterization of the heart and the registration of pressures in heart and great veins have provided a number of new facts about the dynamics of the greater circulation in both normal and pathological states; that the nature of circulatory failure in various types of shock and in congestive heart failure has been somewhat clarified; that tricuspid insuffi-

ciency can be accurately demonstrated; and that with these techniques special opportunity appears to be offered for the study of cardiovascular drugs.

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HUMAN BARTONELLA INFECTION AND AFRICAN SLEEPING SICKNESS*

(Field and Laboratory Experiences)

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It is particularly pleasant that the topic for this evening was delimited to tropical medicine, not alone because it is reassuring evidence of interest in a hitherto rather neglected subject, but chiefly because I believe that the pathology of tropical diseases has not received the attention it warrants from pathologists. Close collaboration between microbiologists, clinicians and pathologists is a commonplace in the fields of what, for want of a better term, we may call "Temperate medicine," but it is still lacking in the tropical field. I hope that this will soon be remedied; I take the invitation tonight as the expression of a similar desire on your part and so may it be. Ample opportunity for the study of tropical material will probably occur with the repatriation of the armed forces.

The French call tropical diseases, "Exotic Diseases," and with your leave I should like to apply this term which fits it so well to Bartonellosis. What could be more exotic, or curious if you prefer, than a disease which is contracted only in certain dangerous valleys, and then only at night; which causes deadly epidemics and kills in three weeks with a fulminating anemia; and which occurs nowhere else in the world but in a small area in South America? Add to this the fact that apparently an entirely different condition which is benign, wherein there is little or no anemia and which is marked by an eruption likewise such as is seen nowhere else on earth, actually is another form of the same disease, and you have an almost incredible story. It is not surprising that those who made the first reports on the subject were treated as medical Munchausens. This story happens to be correct. But the difficulties

* Read January 25, 1945, at The New York Academy of Medicine before the New York Pathological Society.

inherent in proving its correctness will become apparent from a consideration of the history of the disease.

The disease is now endemic in Peru and there is evidence to suggest that it has existed there for a very long period indeed. This evidence antedates the introduction of writing into Peru and is part archaeological and part linguistic.

The archaeological data derive from the pottery. Excavations have unearthed a great quantity of pottery in Peru. Many of these pots or "huacos" are anthropomorphic in design and executed with striking realism. Among these "huacos" some very clearly depict surgical operations, such as trepanation, as well as pathological conditions and deformities. Among these representations of diseased conditions verruga has been identified in pots executed by the Chimu peoples who flourished before the Inca conquest.

At the time the Spaniards arrived in Peru, the natives had a special term in their language, Keshua, to distinguish verruga from the common wart which it somewhat resembles. Written references begin with the Spanish. The very first group of Spaniards on their route south to the conquest of Peru in 1531 were attacked by the unfamiliar disease of "berrugas" at the village of Coaque in Ecuador. Just what this disease was is uncertain, but it is the earliest scriptural record which can be construed to refer to verruga.

The anemic form of the disease apparently attracted little attention until much later, probably because to inspection alone it offered a less distinctive appearance. However, in the late 19th century it was noted that the soldiers who accompanied ore shipments from the mines at Cerro de Pasco to the coast became ill. Many of these guards were Negroes and when, as a contemporary observer put it, the blacks became whites, it was a matter of note.

Medical attention was definitely focused on Oroya fever in 1870 with the outbreak of an epidemic attending the building of the railroad from Lima to Oroya. Deaths among the personnel have been estimated at 7,000 and the epidemic made such an impression on the populace that the saying arose that every cross-tie on the railroad had cost a human life. The nature of the disease was obscure and it was called Oroya fever, although, as a matter of fact, the disease is not contracted in nor endemic in the city of Oroya itself.

The bond between Oroya fever and verruga peruana had not yet

received much consideration. Then, in 1885, Carrión performed the experiment which cost him his life, earned him medical immortality and by giving powerful impetus to the concept of a unitarian etiology profoundly influenced all subsequent thinking on the subject of Bartonellosis.

Daniel A. Carrión was a Peruvian medical student of an inquiring turn of mind who had spent much time studying verruga. He was dissatisfied with the knowledge available and in order to fill certain lacunae resolved to reproduce the disease in himself. He addressed his medical friends and requested them to inoculate him with verruga material. This they agreed to do, but only, according to Carrión's diary, after he had spent some time overcoming their objections. Perhaps his friends were right. After a 21-day incubation period he became ill; the illness progressed very rapidly and it soon became clear that the disease was not verruga. Carrión diagnosed it as Oroya fever, and this result was a complete surprise to him. Unfortunately, after 18 days of illness he died.

It seems clear that, following an inoculation of verruga material, Carrión died of Oroya fever. The conclusion widely drawn was that he had demonstrated the common etiology of the two conditions. The conclusion happened to be correct so that its influence was beneficial.

The causative organism was described in 1905 by the Peruvian physician, Barton, but was not generally accepted as such until the investigations of the First Harvard Expedition were published in 1915.

This report established Barton's bodies as independent organisms; named and gave a full description of them; described the pathognomonic lesion in which they are found in Oroya fever and concluded that they were indeed the etiological agent of this condition.

The cause of verruga was still obscure and it was not until Noguchi and Battistini in 1926 cultivated the organism that the solution was in sight. With this method it was possible to obtain cultures from Oroya fever patients. With these cultures verrugas were produced in monkeys and within the verruga an organism could both be seen and grown which was consistent with that inoculated and with that occurring in human verrugas. Although Noguchi's results were not fully confirmed from other laboratories, the findings of the 1937 Harvard Expedition to Peru supported those of Noguchi, and the unitarian view now seems to be proved beyond any doubt.

In the years 1928-31 Noguchi, Shannon, Battistini and others pro-

duced evidence incriminating the sand-fly, *Phlebotomus*, as the natural vector. This evidence Hertig has recently confirmed, extended and corrected.

So much then for the history of the disease, which indicates to us the long period required to individualize the syndromes, to establish their common cause and to indicate the mode of transmission.

Before proceeding further, a few words on terminology may be useful. Bartonellosis is used tonight to indicate infection with ***Bartonella bacilliformis***. This can be followed by a disease known as Carrión's disease in one of its two manifestations: Oroya fever or Verruga peruana, or, again, no disease may ensue from the Bartonellosis and the infection remains asymptomatic.

The disease occurs in endemic foci in South America only, so far as we know. There, it is limited to the western part being found in certain valleys in the central and western Cordilleras of the Andes chain, between 13° South Latitude and about 4° North of the equator, that is about a thousand miles, comprising parts of Peru, Ecuador and Colombia. Peru is of course one of its strongholds and my own investigations were pursued there as a member of the 1937 Harvard Expedition to Peru, in the hospitals and institutes of Lima where, although the disease is not endemic, many patients are to be found, as well as in the nearby Rimac and Santa Eulalia valleys. It is a pleasure to recall the courtesy and complete coöperation of Doctor Telémaco Battistini through whom facilities for our work were obtained.

In Peru, the type of valley in which the infection prevails is peculiar and has even received the special name of "quebrada." As you may see, they are rather steep and narrow, dry and barren on the sides and tops with vegetation occuring chiefly along the stream bed at the base. But in these valleys there is an additional limit to the disease; it is found only at moderate altitudes. Thus, from sea-level to about 2400 feet the valleys are safe; from 2400 to about 8000 feet the disease is endemic and above 8000 the disease is not contracted. This limitation, we may point out now, is due in turn to the limitation of the insect vector *Phlebotomus* and is subject to some fluctuation according to the season, temperature, humidity and other conditions. Such then is the character of the endemic zone.

As concerns the disease, after a variable incubation period, which is often about three weeks but may be much longer, the initial symptoms

of pain and fever appear. The pains are characteristically those of the bones, joints, and muscles; they are intermittent, often occurring at daily intervals and variable in intensity. The fever may accompany the pain. It is likewise intermittent and variable. It is often mild, not rising above 100.5°F., but on first appearance it may be as high as 104°F., and when accompanied by chills and sweats quite resembles malaria.

This resemblance becomes embarrassing in the case of actual carriers of malaria who are frequent in the region. But the origin of the patient is a clue, as are the pains; quinine is ineffectual, and cultures for *Bartonella* will probably be positive. Actually, diagnosis is rarely made at this time.

From this stage the patient develops, in a period varying from some days to many months, one of the two classical types of Carrión's disease. For convenience and clarity the two will be described separately.

Your Oroya fever patient usually strikes you as being a very sick man when first seen; within a few days you are amazed that he is alive at all. The blood count can fall with startling rapidity and counts of 1,000,000 four days after the apparent onset are recorded. In all severe cases the count is 1,000,000 or below. Even with counts as low as these, the outcome is not necessarily fatal. In one of the patients whom I have seen, the count was 750,000. After some days at this level it began to climb slowly and a few weeks later was near three millions. This patient was apparently on the way to recovery but later died from an intercurrent infection.

The physical examination is not very revealing and the most characteristic finding is the generalized enlargement of the lymph nodes.

The symptoms derive for the most part from the anemia and its effects. The pains and fever of the preceding period intensify but are overshadowed by the rapidly progressing oligocythemia. Pallor is of the most extreme degree, save when mixed with icterus. Vertigo is at first caused by slight movement; soon the same stimulus causes syncope. At night, attacks of pain, fever and delirium render sleep difficult and fitful. Soon, prostration becomes marked and the patient, avoiding all motion, not only from weakness but to lessen pain and faintness, remains in a curiously fixed statuesque position. Finally, with an extreme degree of exhaustion and notable apathy, he awaits the outcome, which is usually evident in from 3 to 5 weeks.

At the time of marked anemia the parasites become numerous in

the blood, and there is a rough proportionality between the degree of the anemia and the number of parasites. More than 90 per cent of the red cells may be parasitized when the count is 1,000,000; whereas bartonellae are rare with a count of 4,000,000. Their appearance is distinctive, and no other human parasite resembles them even slightly. They are stained well by the usual blood stains and then appear as red-violet rods or coccoids situated upon the erythrocyte. They often occur in chain formation suggesting segmentation, and the elements of the chain frequently are at angles with one another giving rise to a V, Y or bayonet appearance. In intense infections they also occur within circulating monocytes and we shall see that they are also to be found in great numbers in the fixed phagocytes of the reticulo-endothelial system.

The other features of the anemia are that it is macrocytic; that the hemoglobin is less reduced than the red cells, giving a color index greater than 1; and that the hemoglobin content of the individual red cell is less increased than its volume, thus qualifying the anemia as hypochromic. Reticulocytes are abundant; in severe cases they may constitute 70 per cent of the red cells. As might be anticipated, liver therapy causes only a slight increase. The blood bilirubin is often, but by no means uniformly, increased. Neither hemolysins nor agglutinins have been found in the serum. There is no hemoglobinuria and, peculiarly enough, all searches for hemoglobinemia have been negative.

In fulminating cases death may occur in 10 days, but the more usual duration of fatal cases is about 3 to 4 weeks. Recovery is usually indicated by an abatement in the fever and a decrease in the number of bartonellae; the red count stabilizes at first, then increases to approach normal values at the end of about six weeks or so, when convalescence begins.

But, the disease almost *never* terminates with the convalescence, and when it does so, this is unpredictable. In the ordinary recovered case, Oroya fever is followed at the end of a variable period, often of about a month, by an attack of verruga peruana.

The prognosis in Oroya fever is not good. About 40 to 50 per cent of the patients may be expected to die, perhaps more in the epidemics. Remissions in the anemia are of favorable import but not invariably so, since relapses occur. It is generally believed in Peru that an abundant florid eruption of verrugas is almost invariably followed by recovery.

The diagnosis of Oroya fever presents no great difficulties when parasites are visible, which they usually are in critical cases. At other times, cultures should be made and the impetus to make them will be received when knowledge of prior residence in the endemic zones, and the history of fever and pain have been obtained.

The microscopic pathology of Oroya fever is just as distinctive in its way as are the parasite and the disease. To my knowledge, there is no other condition in man which gives a similar appearance. If any of you have encountered similar conditions, I should be very glad to learn of it.

At the post-mortem examination, the bodies of Oroya fever patients are of course pale and often somewhat yellow. But what is striking, after the opening of the cadaver, is the enlargement of lymph nodes which has already been noted at the physical examination. These are particularly noticeable in the abdominal cavity but the superficial groups are also involved. Cecal and retroperitoneal nodes of our patients reached 2.5 to 3 cm. in length. These nodes are frequently hemorrhagic and the cut surface shows small areas of red and sometimes of yellow mottling. It is these nodes which present the peculiar microscopic appearance to be described later.

Petechial hemorrhages are rather widely disseminated and this seems to be another of the usual findings. They occur in the skin and conjunctivae; on the surface of the heart; in the pleura and in the lung.

The spleen is frequently normal in size but may be enlarged. Lesions proving to be infarcts are often found. They are yellowish gray or white, are wider at the periphery of the organ than toward the center; are not distinctly wedgeshaped; measure about 1-2 cm. at the surface and extend about 1 cm. into the organ. The liver is more often enlarged than the spleen and usually appears normal even when conspicuous microscopic lesions are present.

The gross pathology is not particularly distinguishing, but when we turn to section material our attention is attracted at once by a unique appearance. This is constituted by the intracytoplasmic development of masses of *Bartonella* within the lining cells of the blood and lymph capillaries. This growth reaches an extreme degree; causes the cytoplasm to expand many times its normal width and then to bulge into the lumen of the vessel. Such distended cells are easily visible in stained sections with the low powers of the microscope. They resemble, at a hasty

glance, nothing quite so much as the endothelial cells during the extreme phagocytosis following blockade of the reticulo-endothelium.

The infected cells are those usually classified as phagocytic endothelium. In addition, heavy infection was noted in the capillaries of the cortical region of the kidneys. The lymph nodes are most often involved but infected cells have also been found in the liver, bone-marrow, spleen, kidney, adrenal, pancreas and occasional cells in the heart and lung.

In one of these patients autopsied by Henry Pinkerton and myself, infected cells were found just below the epidermis and were surrounded by numerous newly formed capillaries and a few proliferated endothelial cells. These last two findings: newly formed capillaries and proliferated endothelial cells are characteristic of the verruga state of Bartonellosis, while the infected swollen vascular lining cells are the earmark of Oroya fever. To find them associated is of interest, since it indicates what is probably the transition between the two very distinct pathological appearances.

In Oroya fever, within the infected cell the entire cytoplasm may be filled with parasites. The distribution is usually not uniform, for bartonella tends to form rounded masses or clumps. Within Kupffer cells of the liver there is less of a tendency to clumping and the majority of infected cells may show discrete organisms only. While the nuclei are at times obscured and distorted by masses of parasites which may lie upon the nuclear membrane, bartonellae have not been observed in a distinctly intranuclear position.

The lesion was absent in one of our patients who, after recovery, died later of toxoplasmosis, but was present in two others who died of Oroya fever. Our data and evidence in the literature suggest that it is only when the blood infection is heavy that the stuffing of the endothelial cells occurs.

Other lesions which have been found are less distinctive, in the lymph nodes and spleen, infarcts have been observed. It is thought that these follow upon vascular occlusion by the swollen endothelium. In the liver, although we did not observe it, areas of necrosis localized about the central veins have been reported. The bone marrow shows signs of energetic hematopoiesis.

The pathogenesis of the anemia is not well understood in its details. All of the evidence suggests that increased erythrocyte destruction occurs, but the mechanism producing the blood loss is obscure. Notably,

no lytic substances have been demonstrated either *in vivo* or in cultures. The bone marrow is very active, the reticulocyte count high and poor hematopoiesis cannot be invoked, save in a few cases and these appear to be secondary to the blood loss.

Very unfortunately animal experimentation is of little aid to us in connection with this problem, since Oroya fever can be reproduced only incompletely in an occasional *rhesus* monkey, and yet this animal, unsatisfactory as it is, is the best which is known. This again is inexplicable at present, for in the *rhesus* monkey, the verruga form of the disease caused by the very same organism can be reproduced at will.

Such then is Oroya fever which we may now define as a febrile anemia of rapid evolution and high mortality caused by *Bartonella bacilliformis*, and characterized pathologically by the distension of vascular endothelial cells with masses of parasites.

If the patient recovers from Oroya fever it is usually only to be attacked by the disease in its other form, verruga peruana, which we will now consider.

A patient with a profuse florid eruption of miliary verrugas is an unforgettable sight. Imagine, if you will, a person studded over with innumerable cranberries, the "berries" varying in color from red to purple, and you will gather what a very striking picture this is.

There is a considerable degree of variation and three types of verrugas are distinguished according to size and situation; miliary, nodular and "mulaire." The miliary type projects above the surface of the skin and is small, measuring about 1 cm. in greatest diameter. The nodular variety is more deeply seated in the skin and subcutaneous tissues, is larger, and does not at first project above the skin surface. It may, however, during the course of its evolution press against the skin and finally erode it, in which case it is known as a "mulaire" verruga from a resemblance to a lesion seen in mules.

The three kinds frequently occur together and since the eruption takes place by successive crops, verrugas of all types and at all stages of development and regression may be seen on the same patient.

The eruption occurs on covered and exposed areas alike. The regions of predilection are the limbs and face; they are rarer on the genitalia and scalp. They may occur on the mucosae and I have seen a patient with a profuse skin eruption present entirely analogous papules on the tongue and the roof of the mouth where they later become confluent.

However, the numerous reports in the literature of "internal verruga" occurring in the spleen, heart, brain, and other organs should be received somewhat critically, for there is no doubt that other lesions have been misdiagnosed as these internal verrugas.

The eruption persists from one month to two years. The miliary lesions are the first to disappear, and unless infected leave no cicatrix; the mulaire verrugas persist longer and with these, scar formation is the rule. The accompanying signs and symptoms are not conspicuous. There is some pain and fever and a moderate degree of anemia. The prognosis is good and uncomplicated verruga is very rarely fatal. Quite exceptionally Oroya fever may occur after verruga and carry off the patient.

A generalized well developed verruga eruption has an extremely distinctive appearance. The clinical diagnosis may be confirmed by the demonstration of bartonellae in the lesions and cultures from the blood are usually positive.

In sections there are three findings which typify the verruga: numerous new-formed small-caliber blood vessels, proliferated endothelial cells and *Bartonella*. The endothelial cells tend to occur in masses or islands lying in edematous connective tissue, the whole being infiltrated by a variable number of lymphocytes, plasma cells and polymorphonuclears. The bartonellae are conspicuous bright-red bacillary or granular structures when stained by the Regaud-Giemsa technique. They are situated in the neighborhood of, or within, endothelial cells. The formation of rounded masses of bartonellae within the vascular lining cells leading to distension of the latter, such as is seen in Oroya fever, is altogether uncommon in verruga.

With these three features in mind it should be possible to distinguish verruga from the majority of skin lesions with which it has been compared, such as secondary yaws, warts or molluscum contagiosum. The resemblance of verruga to telangiectatic granuloma is said to be striking, but bartonellae are not found in the latter.

The only real difficulty arises with an entity known as Bassewitz's tumors, also called "angiofibroma cutis circumscriptum contagiosum." This resembles verruga and in some cases objects which were called inclusions have been observed. It may be that some of these pseudoverrugas really are verrugas and, if this is the case, then the geographic distribution of verruga may be far wider than we know it today.

Experimental verruga is easily produced in the rhesus monkey and

the lesion almost exactly reproduces the one seen in man. Successful inocula may be cultures, or verruga tissue, or tissue from Oroya fever. Inexplicably enough, blood, even when it contains enormous numbers of organisms and is injected in large amounts, will almost invariably fail.

These then are the two forms of Carrión's disease: verruga and Oroya fever. But in addition Bartonellosis may exist as an asymptomatic infection of no interest to the clinician perhaps, but of enormous importance epidemiologically. In the village of Callahuanca, where the disease is endemic, we undertook the first surveys to be made of the incidence of infection in the healthy population, using blood cultures for this purpose. You have seen the type of house which exists there; it seems almost incredible that sterile bacteriological work could be carried out in such surroundings. But so it turned out, our contaminations, surprisingly, were very low and we found that about 10 per cent of the population were carriers of *Bartonella*. Similar figures have since been obtained by others. From this and other data it appears that *man* is the chief reservoir of *Bartonella* and since these carriers are often perfectly healthy, probably the chief transporting agent as well.

Concerning *Bartonella bacilliformis* some data have already been presented. The organism bears a resemblance to the *Rickettsia* of epidemic typhus in its morphology and in its development within the cytoplasm of cells. *Bartonella*, however, can be propagated indefinitely in cell-free medium. The morphology in the blood has already been seen and it is here that variation is most marked, rods, coccoids and rings can all be observed, sometimes in the same patient.

The culture medium usually used is the semi-solid agar containing rabbit serum and hemoglobin employed by Noguchi and Battistini in their pioneer work in 1926. In this medium growth is apparent in 10 days or so in a zone approximately 1 cm. wide which occurs about 1 cm. below the surface.

Colonies may be macroscopic and appear as white rounded masses rarely larger than a millimeter in diameter, or the growth may be more scattered and appear as a faint halo. Growth is optimal at P H 7.8 and at 28°C. Of its metabolic activity in culture, the fact that it does not hemolyze red cells is perhaps the most interesting. In tissue cultures *Bartonella* develops within the cell cytoplasm and also extracellularly; in the insect vector the localization is not yet definitely known.

Some strains are motile and in connection with these, flagella have been described. There are no spores nor capsules. Reproduction takes place by binary fission and there is no evidence of a complex life cycle, such as once was considered evidence of the protozoan nature of *Bartonella.*

Bartonellosis is an insect-transmitted condition. The only proved vector is the sand-fly or *Phlebotomus.* In Peru it is the species *verrucarum* which is responsible and the peculiar epidemiological features of the disease are closely linked to the biology of *Phlebotomus verrucarum.* This fly measures about 5 mm. in length. It is consequently quite small and will pass through the ordinary mesh mosquito netting. The raised position of the wings while at rest is quite characteristic. Being whitish in color and since it is seen chiefly at night, the term "ghost gnat" seems peculiarly appropriate. Only the female takes blood.

In the infected quebradas it is captured in the vicinity of human habitations. Like man, the fly fears excessive dryness and both animals therefore gravitate to the more humid areas near the streams at the bottom of the valley.

The old report that verruga is contracted only at night in Peru is substantially correct. These phlebotomi do not like light and are active only from dusk to shortly after sun-up. I, and a great number of other investigators have spent time in the verruga zone, restricting our visits to day-light hours without becoming infected. The fly can, however, be captured during the daytime by disturbing it in its natural hiding places, such as caves and rock crevices.

The limitation of the disease to moderate altitudes is correlated with the distribution of the vector. Above the upper limit, the night temperature seems to be too low for the fly. Below the lower limit, the humidity is probably not great enough. These data have been obtained in Peru where the most careful entomological investigations have been carried on.

On a basis of this information, the restriction of Bartonellosis to a limited area in South America was once explained, on the assumption that only Peruvian sandflies were good vectors. However, this assumption was gratuitous, being completely unsupported by experiment. In the late 1930's an epidemic broke out in Colombia which was finally identified by Dr. Patiño Camargo as Oroya fever. There, the epidemiology is similar to that occurring in Peru, and *Phlebotomus* has been

taken in the bartonella area. But from Colombia a fact of the very highest importance has been brought to light.

This is, that none of the phlebotomi incriminated in Peru has thus far been found, so that, although the common vector is not yet known, it seems altogether likely that it is not the same in Colombia as in Peru. From this we may conclude that *Bartonella bacilliformis* is not strictly limited in its insect host. This datum further suggests that the epidemic took place by the introduction of *Bartonella bacilliformis*, possibly through carriers, rather than by the acclimatization of infected foreign sandflies.

The question immediately arises as to the suitability of still other sandflies as vectors. Since the species of these insects which feed on man are widely distributed throughout the world in tropical and subtropical areas, the question is not without its importance. In the United States very recent investigations have shown that *Phlebotomus* is more widely represented than was known previously and at least one species, *Phlebotomus diabolicus*, found in Texas, is a known human feeder.

This question has, so far as I am aware, never been attacked experimentally. From our knowledge of the biology of *Bartonella bacilliformis* however, and by analogy with other insect-borne diseases caused by microörganisms, there is no reason to suppose that a number of species of *Phlebotomus* would not prove to be suitable vectors. Certainly the data obtained from Colombia support this view. And we also know that human carriers are capable of introducing *Bartonella* into hitherto uninfected areas.

Concerning the possibility of spread, there is then no reason for complacency. The factors which have limited the disease in the past appear to be first those natural environmental circumstances which have limited the distribution of phlebotomi and secondly the absence of mass movements of the infected populations.

Man very rarely found it possible or expedient to affect the phlebotomi adversely, although it should be admitted frankly that he has not expended any considerable effort in this direction. As a result of this attitude, it is probably true that human activities have tended, on the whole, toward extension of the disease where extension was possible by the introduction of carriers into phlebotomus-infected zones. We have depended, it might be said, on Nature to protect us and Nature is not obviously partial to the human species.

In closing this presentation concerning Bartonellosis, I note an oversight: I have neglected to discuss the therapy of Carrión's disease. But this is readily summarized; no effective etiological treatment exists.

African trypanosomiasis, the second disease to be considered this evening, has had a most notable retarding effect on the development of Central Africa. If it be considered that the Continent was known before Western Europe had felt the impact of Roman civilization and that Carthaginian traders were active on the West Coast of Africa, one cannot fail to be impressed with the contrast between the present development of Central Africa and that say, of the Americas, discovered so many centuries later.

This retarded development recognizes many causes: climate, disease, etc. But the part played by the trypanosomiases of man and animals—not only by decimating human populations but through epizoötics which have rendered animal husbandry difficult or impossible—is not easy to over evaluate.

Even today, after many years of sustained effort directed against the disease, the morbidity it causes it still very considerable. Thus in Gambia in 1936, 40 per cent of the in-patients were affected with sleeping sickness, which caused 30 per cent of the hospital deaths. The total number of cases is unknown, but a recent report from the League of Nations states that 1,000,000 African natives are under treatment and it is scarcely possible to make even an estimate of the number of undiagnosed cases.

We in the Americas are certainly fortunate that the sleeping sickness has never taken a foothold here. The disease has been introduced and probably innumerable times, at the time of the slave trade, but has never become endemic. This, of course, was due to chance, not to foresight. It so happens that the only known vectors which allow the trypanosomes to go through their complete cyclical development are the tsetse flies of the genus *Glossina*, which now exist only in Africa.

However, such has not always been the case. At one time the tsetse fly existed in the United States, for fossils of a long extinct species have been found in miocene deposits in Colorado. That *Glossina* has died out in the Americas seems clear, why they died out is not so evident, and whether if re-introduced they would be able to acclimatize themselves is completely unknown. Among all these uncertainties, one thing, however, is known. *Glossina* has been transported by air to South Amer-

ica, since dead tsetse flies have been taken in the pools of insects obtained after fumigation of airplanes making the South Atlantic crossing.

The possibility of the establishment of African trypanosomiasis in the Americas is remote. It will not take place from the introduction of infected individuals alone, it may take place should the flies ever become established and both flies and patients be present together.

In Africa, the only continent where the disease exists, it is very widespread, extending roughly from Dakar in Senegal to Angola on the West Coast, and from the Southern Sudan through Rhodesia in the east.

If the map be studied attentively, it will be noted that strongholds of the disease are found along the great river systems, the Congo and its tributaries, the Volta, and so on.

This is so, because one of the chief vectors, *Glossina palpalis*, and some of the other vectors congregate along the rivers.

I was given a beautiful demonstration of how water fits into the epidemiology of sleeping sickness at a village in the Kasai region of the Belgian Congo situated on a small river which was one of the tributaries of the Congo. The white planter had his home placed on a hill, less than a mile away from the river and almost never saw a tsetse fly there. He considered the risk so slight, that although he had invested in an electric generating plant, a frigidaire, etc., he had never considered it necessary to install screens.

Yet, at the ford on the river, the glossinas were abundant. Now to travel from the village to the nearest city it was necessary to cross the river, which was done in a dug-out canoe, handled by a native ferryman. One was no more than a few feet out when the tsetses began to appear in great numbers. In the crossing, which took at the outside perhaps 5 minutes, at least a dozen tsetses attacked the white missionary seated in front of me. And on our landing on the opposite side we encountered masses of the flies. My companion, in a few minutes' time, captured a dozen on my back, and probably missed as many more, and all the while I was extremely active brushing still others off my sleeve, pant-legs, etc.

So much then for what the fly density may attain. It seemed perfectly clear that no one could spend any time at the river without undergoing the most serious risk of being bitten, even when clothed. But the natives, I remind you, were almost totally unclothed.

And for the natives a great deal of their activities were carried on at

the water's edge. There they bathed, there the washing was done—the mothers taking the children along so they could watch after them—and there the villagers went for their daily supply of water.

So you had what was almost an ideal situation—epidemiologically speaking—for transmission. Infected persons, flies and non-infected individuals juxtaposed and the same circumstances repeating themselves over and over again at almost daily intervals. Cases of the disease were not yet frequent, but the local health officer feared, and I think quite rightly so, that an explosive outbreak might occur at any time.

It is frequently stated that the tsetse prefers black skins to white ones. From my experience this is no cause for easiness. Either the flies were misled by the dark color of my clothing, or their color perception was poor, but whatever the explanation, the continued attention of dozens of the flies was to me satisfactory evidence that the flies considered me as succulent a dish as was to be found in the neighbourhood.

My own recent experience with sleeping sickness was obtained as a member of an expedition organized under the joint auspices of Harvard University and The American Foundation for Tropical Medicine. It derives chiefly from a stay in Liberia at the hospital of the Firestone Plantations Company at Harbel, where facilities were very kindly made available for my work, and from a visit to the Belgian Congo where an opportunity was offered to study a focus in the interior, and to become acquainted with the investigations carried out in the splendid central research Institute at Léopoldville.

Two of the signs and symptoms of sleeping sickness are conspicuous to everyone, the enlarged lymph nodes and the somnolence. By reference to these, some idea as to its history may be pieced together. As far as I have been able to learn, the earliest reference known is that of an Arab writer Al-Qualquashaudi, of the 14th century.

One strong impetus to its study was an economic one, and with the advent of the slave-trade it became realized—at least on the part of the shrewder traders—that natives with enlarged cervical nodes were a poor investment, since they were likely to die on the long trip across the Atlantic. It may well be that this clue was obtained from the Africans themselves, for in certain regions the natives practised extirpation of the enlarged nodes, apparently believing that the latter were the cause of the disease they accompanied.

From the middle of the 18th century on, various travellers mentioned

the disease and the name of one of these, Winterbottom, has been retained in the designation Winterbottom's sign, to denote the enlarged cervical nodes.

One other of these travellers is of particular interest and that is the journalist Stanley. On his famous trip in search of Livingstone, he organized his party, obtained his carriers, etc. in West Africa, and then proceeded cross-continent to the vicinity of Lake Victoria. By many authorities, it is believed that the natives he brought with him introduced the disease into Eastern Africa, giving rise to the terrible epidemics which in certain areas of the lakes region destroyed two-thirds of the population in eight years.

The important scientific discoveries were not made until after Africa was carved up into its various colonies.

In the 1890's Bruce showed that "nagana," an important disease of cattle and game, was caused by trypanosomes and carried by tsetse flies.

Forde and Dutton in 1901 and 1902 observed a peculiar case of pyrexia in a resident of Gambia, studied him carefully and discovered trypanosomes in his blood. The latter year Castellani observed trypanosomes in the spinal fluid of somnolent persons. Some of these patients also had the organism in the blood, which indicated the bond between the febrile and the somnolent forms.

The role of the tsetse, suspected by the natives, was proved by Bruce and Nabarro in 1903. However, it was not until the work of Kleine in 1912 that it was clearly realized that the trypanosomes underwent cyclical development in the tsetse, that during a period of their multiplication they were non-infectious, but after various structural changes finally migrated to the salivary glands, where as the so-called metacyclic forms they produced infection when injected by the bite of the fly.

An early successful therapeutic agent was atoxyl, the pentavalent arsenical synthesized by Pasteur's great rival Béchamp. Tryparsamide, synthesized by Jacobs and Heidelberger, and introduced into therapy by Louise Pearce, is an improvement and remains today one of the two standard drugs used in this disease.

The other is a Bayer product, Bayer 205, known also as Antrypol and Naphuride. This is a non-metallic drug similar to the benzidine dyes. It is very effective in the early stages of sleeping sickness and has itself a highly interesting history, being one of the few drugs which has earned a place in politics as well as in therapeutics. Its political status

came about as follows: The drug was produced after the last war and the Germans, knowing that they had something valuable, kept its composition secret. The reason for this was revealed when one of the men familiar with it gave an address, in which he stated that Bayer 205 was the key to the successful colonization of Africa, that its structure should accordingly be kept secret and the only price to be accepted for its revelation was the restoration of some of the colonies Germany lost during the last war. This plan was not successful, for although the Germans published enthusiastic reports on 205, the rest of the world wanted to test it themselves. Finally, in an impasse, the Germans furnished some for trial. A small amount came into the hands of the chemist Fourneau in Paris, who promptly synthesized it, published the formula and thus made it available to all.

In regard to the disease, the first symptoms may result from the infecting bite itself. I have only seen one such case. At the site of the bite a reaction was visible at the end of about 24 hours. It increased during the next 24 to 48 hours and then consisted of a reddened edematous area about 3 inches in diameter, slightly raised and hot to the touch, but not painful on palpation.*

At this time trypanosomes could be found in the area by puncture. The lesion then regressed and at the end of a week was inconspicuous. It is said that this lesion may sometimes progress, become necrotic and persist for a long while.

From the time of the infecting bite a variable period intervenes before complaints are voiced. In Liberia, where the disease seems mild in type, this period may extend over several months and many of our patients were picked out because of enlarged lymph nodes when they stated that they felt perfectly well. Elsewhere, the progress is more rapid and fever is noted at the end of a few weeks.

The fever may be intermittent or remittent, but characteristically is very irregular. It is said to be more common in whites. The pulse is rapid and remains so during apyretic periods.

The enlargement of the lymph nodes is a sign of more frequent occurrence. It rarely reaches the pigeon egg size, which, because of its photogenic qualities, is so often used in illustrations, and the nodes are more often about 1 cm. or 15 mm. in greatest dimension. They are at first soft and succulent; later becoming hard and fibrous. Winterbot-

* Uninfected flies may produce similar reactions in sensitive individuals according to some reports.

tom's sign consists in the swelling of the posterior cervical nodes; the epitrochlears and supraclaviculars are also often enlarged. These swollen nodes frequently contain trypanosomes, particularly at the soft and succulent stage, and puncture of these nodes is one of the principal methods of diagnosis.

Skin eruptions are said to be frequent in whites. My patients were all negroes and I did not observe any skin eruptions. Pruritus was common, and is described in sleeping sickness, but it was difficult to assign its true cause, since a dermatitis, a form of craw-craw, believed to be caused by chronic infection with the itch-mite, *Sarcoptes scabiei*, was almost universal. Edema of the face or of the eyelids or about the hands, feet and joints is common.

Such then are the signs and symptoms of the early stage of sleeping sickness. At this time trypanosomes may be found in the blood and lymph nodes; they usually are absent from the spinal fluid. Treatment instituted at this period has a good chance of success; later the prognosis is much more dubious.

From this stage the patient gradually passes into the period of nervous involvement.

Changes in the sleep pattern occur early. At first it may be nocturnal insomnia with diurnal somnolence, and be somewhat difficult to assign to its true cause. Deep hyperesthesia is frequent, and the turning of a key in a lock my give rise to a pain which is hardly bearable.

Then, as time progresses, in periods varying from a few months to a few years, the disease evolves and the patient presents the classical picture of sleeping sickness. He is dull and apathetic; he comprehends poorly, he is disinclined to exertion and frequently goes to sleep even in the sunlight, and this sleepiness so masters him that he fails to awake even for the necessities of food and cleanliness.

Upon examination, tremors of the tongue and fingers are frequently noted. The gait is peculiar, often with shuffling, but in general there is no paralysis. There may be clonus of the ankle or patella. Romberg's sign is frequently positive. Headache is a common complaint and frequently psychical changes manifested by delusions, hysteria and attacks of mania are noted.

As the disease progresses, these symptoms become more marked, emaciation of extreme degree will occur if excellent nursing does not prevent; bedsores form, the blood pressure falls and the patient passes

away in coma.

The duration of the cerebral stage is from a few weeks to a few years.

These symptoms are frequently dissociated. I recall distinctly a woman with trypanosomes and over a thousand cells in her spinal fluid, who was bright, alert and responsive. She did not sleep very much and gave no evidence of any psychical disturbance. She did have hyperactive reflexes, an ankle clonus and Romberg's sign, so that her complaint was that she walked badly. Since I was interested in evaluating a hitherto unused drug, this patient seemed a most interesting case to try it on. But to my great disgust, after the treatment was only half completed, her walking had so improved that she left the hospital and walked home.

The elements of the clinical diagnosis have already been given. Trypanosomes are found in the blood and lymph nodes in the early period; and since either may be negative, both should always be examined. In the cerebral stage the parasites occur in the spinal fluid, but usually only after a significant rise in the cell count.

If all these examinations are negative, the inoculation of guinea-pigs and rats may be essayed—it may, however, often be negative with strains of low virulence such as are found in Liberia.

Cultures, in which I am particularly interested, may be resorted to, but they are not yet suitable for routine use.

The earlier the diagnosis can be established, the better the prognosis. Treatment initiated in the early stages often cures the patient; in the cerebral stage not only are the trypanosomes more difficult to eradicate, thus requiring higher doses—a decided drawback with a toxic drug—but if tissue damage is too marked, it may not be possible to restore normal function. Untreated cases almost always die, although there are some reports of spontaneous cures. As pointed out before, there are variations in the severity of the disease in different areas.

I was not able to obtain any autopsy tissue in Liberia, and the following pathological account is based on the reports of others.

Lesions of the lymph nodes and the central nervous system are those most constantly observed. The lymph nodes are enlarged, particularly those in the posterior cervical, epitrochlear and supraclavicular regions. Microscopically, the follicles appear enlarged and an infiltrate is present, composed of polymorphonuclear and plasma cells. At times the so-called "morula cells," to be discussed subsequently, may be found. Later the

nodes become sclerotic and there is marked growth of connective tissue.

The brain is the site of a widespread encephalitis, found in both the white and grey matter, with extremely marked infiltration around the vessels. This perivascularitis is distinguished by the predominance of plasma cells which is said to be greater than that observed in any other infection. In addition to plasma cells the infiltrate is said to be composed of neuroglial and microglial elements mixed with macrophages of meningeal and monocytes of vascular origin. The vessels themselves show some swelling of the endothelium, but no endarteritis or thrombosis.

In addition to the perivascular infiiltration, the presence of the so-called "morula cells" of Mott in considerable numbers is characteristic. These are derived from plasma cells and are now thought to be identical with Russell bodies, which they very much resemble. Accordingly, while they are characteristic of sleeping sickness, they are no longer thought to have any specificity.

The meninges are sometimes thickened and usually show a widespread perivascular inflammatory lesion similar to that described in the brain.

Trypanosomes can be demonstrated in sections after fixation with alcoholic sublimate and staining with Giemsa's solution according to Wolbach's technique. For certain authors the organisms are present in the brain and with sufficient constancy to suggest a direct cause and effect relationship to the lesions, but this is by no means a universally held opinion. The problem does not appear to have been studied very exhaustively in man, and it would seem that here is a situation where collaboration between microbiologists and neuropathologists might be fruitful.

The trypanosomes of African sleeping sickness are flagellate organisms readily detectable in blood or lymph node fluid by their active movements.

The only human parasite with which they are likely to be confused is *Trypanosoma cruzi*, which causes the so-called "American trypanosomiasis," or Chagas' disease. But *Trypanosoma cruzi* is morphologically different, has an intracellular tissue stage in man, is readily cultivated and has a quite different vector.

The African trypanosomes readily become arsenic-fast and it is known that this drug resistance persists after passage through the fly.

It is easily understood therefore how an arsenic-fast strain may be found in certain areas, and accordingly why dosages of arsenicals used in treatment may vary considerably from one region to another.

An interminable, and to my mind tiresome and fruitless discussion has been carried on for years as to whether more than one species of trypanosome is involved in sleeping sickness. Everyone agrees that *Trypanosoma gambiense* is a good valid species, but they are not agreed about *Trypanosoma rhodesiense*, which does differ biologically, but not morphologically. Since there is no common agreement amongst protozoologists as to the validity of biological species, the discussion is likely to rage unabated indefinitely. It may be noted, however, that the unicists do not push their argument to the logical extreme and identify the human trypanosomes with a morphologically indistinguishable organism *Trypanosoma brucei*, which does not infect man. They are right, it seems to me, on a basis of convenience, and for the same pragmatic reason I believe *Trypanosoma rhodesiense* should receive a separate designation; whether that be of specific rank or not, is of far less importance.

The epidemiology of the disease involves chiefly man and the fly. Man is the important reservoir of the infection it seems, wild animals, such as the sitatunga antelope (*Tragelaphus spekei*), playing a subsidiary role in this respect. However, the fact that a domestic animal, the pig, may harbor the infection and be capable of infecting flies, is of considerable interest in those regions where hog-raising is common.

Wild animals do play a part in furnishing nourishment to the flies which are quite catholic in their tastes. Many authors, impressed with this fact, have proposed widespread destruction of game to control the flies, but, in the absence of protection of man, this measure may have just the contrary effect from that intended.

The anti-fly measures which have been used are innumerable, and it would seem that almost no method was too fantastic not to have had some proponents. The great Robert Koch, for example, impressed with the fact that *Glossina* would feed on crocodiles, proposed the systematic destruction of crocodile eggs as a means of controlling the flies in Africa.

Actually the methods in use have to vary according to the *Glossina* they are directed against. While a number of species are good vectors, they can be classified roughly into the hygrophile group exemplified by *Glossina palpalis*, which is found in the vicinity of water, and the

xerophile group, such as *Glossina morsitans*, which can live under much drier conditions.

Clearing vegetation along river banks, particularly at fords, village sites and other places of congregation has proved effective against *Glossina palpalis*. Against the forest and savannah species, resettlement of villages in burned over areas, which are subsequently put under cultivation, has been beneficial.

For the protection of the individual, a development in the last year is of more promise than anything which has happened in a very long time.

This is a method of chemo-prophylaxis originated and now under study in the Belgian Congo. van Hoof and his collaborators studied the effect on African trypanosomiasis of Pentamidine, a new drug now coming into use in kala-azar. In *treatment* it was not superior to drugs already in use. But carrying their experiments further, they noted that, in animals, single injections would confer protection against the fly-borne disease, this protection extending over many months.

The method was extended to man, first with laboratory experiments on two volunteers. These men received a single intramuscular injection of Pentamidine and then infected flies were fed on them every 2 or 3 days for about a year, until the men became positive. This took 295 days for one man; the other did not become positive until 12 months after the injection. Both of these men were blood positive, the cerebrospinal fluid was examined in one at the end of the experiment and found normal.

At the time I was in the Congo, that is, in June, the early results of the first field trial were known. The results indicated that protection was obtained from a single injection of 2 to 3 milligrams of Pentamidine per kilogram of weight for a period of 6 months. Given intramuscularly, the drug was not notably toxic and the protective results obtained were markedly superior to those given by Bayer 205.

The method is too new as yet, and has been tried on too few people for any firm conclusion to be drawn as to its value. But should the promise of effective mass prophylaxis, following a single injection every six months, be kept, it may well change the whole complexion of the sleeping sickness problem in Africa.

Another recent discovery of interest is that pyrethrum is an effective tsetse repellent. A preparation in a vanishing cream base prevented

tsetses from biting for periods varying from 2 to 6 hours, depending on the rate of perspiration. Repellent is perhaps not quite the right word, for the flies alighted readily enough, but did not take blood. Pyrethrum, it thus seems, can be of service in individual prophylaxis.

The treatment remains what it has been for some time: Bayer 205 and tryparsamide, given either separately or more often nowadays, in succession. The usual treatment consists of a course of Bayer 205 to total 10 grams, 1 gram being given intravenously once or twice weekly. Then after a two-week rest tryparsamide is administered—1 gram the first dose, then 2 grams, once or twice weekly to total 15 to 25 grams, or more, depending on the response.

New developments in therapy comprise several arsenical compounds which now past the experimental stage, have been tried clinically. One of these is Melarsen oxide, a trivalent arsenical compound. The initial results which my patients showed were encouraging; the drug is effective in both the blood and cerebral stage and appears to be relatively non-toxic. But in a chronic disease, such as trypanosomiasis, results can only be judged after years of careful study, and whether Melarsen oxide presents advantages over drugs now in use, is not yet known.

The amidine compounds are being used prophylactically as I have described; their use in therapy is on the wane.

As for penicillin and the sulfonamides, unfortunately sleeping sickness is one of the diseases in which they have produced no spectacular effect.

In closing, I wish to express the hope, that by pointing out certain unsolved problems in the two diseases discussed tonight, that this presentation may serve in some sort as a stimulus to the investigation of those tropical conditions which soon now will come to your notice.

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*R. H. Follis, D. Jackson, M. M. Eliot, and E. A. Park: Prevalence of rickets in children between two and fourteen years of age, Am. J. Dis. Child. 66:1-11, July 1943.

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